



US009457036B2

(12) **United States Patent**
Dahl et al.

(10) **Patent No.:** US 9,457,036 B2
(45) **Date of Patent:** *Oct. 4, 2016

(54) **COMPOSITIONS AND METHODS FOR COMBINATION ANTIVIRAL THERAPY**(71) Applicant: **Gilead Sciences, Inc.**, Foster City, CA (US)(72) Inventors: **Terrence C. Dahl**, Sunnyvale, CA (US); **Mark M. Menning**, San Francisco, CA (US); **Reza Olyai**, Foster City, CA (US)(73) Assignee: **Gilead Sciences, Inc.**, Foster City, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 59 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/523,758**(22) Filed: **Oct. 24, 2014**(65) **Prior Publication Data**

US 2015/0111855 A1 Apr. 23, 2015

Related U.S. Application Data

- (63) Continuation of application No. 14/227,653, filed on Mar. 27, 2014, which is a continuation of application No. 12/204,174, filed on Sep. 4, 2008, now Pat. No. 8,716,264, which is a continuation of application No. 10/540,794, filed as application No. PCT/US2004/000832 on Jan. 13, 2004, now abandoned.
- (60) Provisional application No. 60/440,246, filed on Jan. 14, 2003, provisional application No. 60/440,308, filed on Jan. 14, 2003.

(51) **Int. Cl.**

A01N 43/54 (2006.01)
A61K 31/505 (2006.01)
A61K 31/675 (2006.01)
A61K 31/513 (2006.01)
A61K 31/7076 (2006.01)
A61K 45/06 (2006.01)
A61K 31/683 (2006.01)
A61K 9/20 (2006.01)

(52) **U.S. Cl.**

CPC *A61K 31/675* (2013.01); *A61K 9/2009* (2013.01); *A61K 9/2013* (2013.01); *A61K 9/2018* (2013.01); *A61K 9/2054* (2013.01);
A61K 9/2059 (2013.01); *A61K 31/513* (2013.01); *A61K 31/683* (2013.01); *A61K 31/7076* (2013.01); *A61K 45/06* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56)

References Cited

U.S. PATENT DOCUMENTS

3,524,846 A	8/1970	Moffatt et al.
3,622,677 A	11/1971	Short et al.
3,682,930 A	8/1972	Bourquin et al.
3,994,974 A	11/1976	Murakami et al.
4,003,878 A	1/1977	Skaar et al.
4,258,062 A	3/1981	Jonas et al.
4,355,032 A	10/1982	Verheyden et al.
4,384,005 A	5/1983	McSweeney
4,430,343 A	2/1984	Iemura et al.
4,476,248 A	10/1984	Gordon et al.
4,724,233 A	2/1988	De Clercq et al.
4,808,716 A	2/1989	Holy et al.
4,816,570 A	3/1989	Farquhar
4,879,288 A	11/1989	Warawa et al.
4,935,507 A	6/1990	Takaya et al.
4,957,924 A	9/1990	Beauchamp
4,968,788 A	11/1990	Farquhar
5,047,407 A	9/1991	Belleau et al.
5,075,445 A	12/1991	Jarvest et al.
5,142,051 A	8/1992	Holy et al.
5,151,426 A	9/1992	Belleau et al.
5,155,268 A	10/1992	Hester

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0 182 024 A2	5/1986
EP	0 206 459 A2	12/1986

(Continued)

OTHER PUBLICATIONS

Gild—Gilead Sciences Conference Call to Discuss Triangle Pharmaceuticals Acquisition dated Dec. 4, 2002, Ristig et al. (Tenovofir Disoproxil Fumarate, TDF) Therapy for Chronic Hepatitis B in Human Immunodeficiency Virus/Hepatitis B Virus—Coinfected Individuals for Whom Interferon-alpha and Lamivudine Therapy Have Failed, JID 2002; 186 pp. 1844-1847.*
Memorandum Opinion and Order Construing Patent Claims, signed by Judge Irene M. Keeley, Case No. 1:14-cv-00099-IMK (Dated: May 12, 2015), 44 pages.

(Continued)

Primary Examiner — Alton Pryor*(74) Attorney, Agent, or Firm* — Cooley LLP(57) **ABSTRACT**

The present invention relates to therapeutic combinations of [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester (tenovofir disoproxil fumarate, Viread®) and (2R,5S,cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine, Emtriva™, (-)-cis FTC) and their physiologically functional derivatives. The combinations may be useful in the treatment of HIV infections, including infections with HIV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors. The present invention is also concerned with pharmaceutical compositions and formulations of said combinations of tenovofir disoproxil fumarate and emtricitabine, and their physiologically functional derivatives, as well as therapeutic methods of use of those compositions and formulations.